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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,883	SWANSON ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,10-12,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *34* is/are allowed.

6)☒ Claim(s) *1,4-8,10-12 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/5/10 has been entered.

Applicants' Amendment and Remarks, filed 4/5/10, have been entered. Claim 1 and 12 amended; claims 9, 13, 30-32 are cancelled; claims 33-34 are newly added; claims 1, 4-8, 10-12, 33, 34 are pending and under current examination.

Election/Restrictions

Applicant's election of Group I (claims 1-13) in the reply filed on 4/15/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/15/09.

Claim Objections

Claims 4-8 are objected to because of the following informalities: The claims recite that the treating comprising reversing the mis-splicing of various proteins. Splicing occurs at the gene level, therefore, the claims should read that the treating comprises reversing the mis-splicing of a specific gene (*e.g.*, the Clcn1 skeletal muscle chloride channel gene, in claim 4). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8, 10, 11 and newly added claim 33 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of reducing **myotonia** in the muscle of an individual suffering from myotonia (or myotonic dystrophia), comprising intramuscular injection of a recombinant adeno-associated viral (rAAV) vector comprising a promoter operably linked to a nucleic acid encoding muscleblind1 (MBNL1) protein, wherein expression of the MBNL1 protein results in reducing **myotonia** in the muscle of the individual.

The specification does not reasonably provide enablement for:

1) Treatment of any other symptom of myotonic dystrophia, other than myotonia;

2) The reversing of mis-splicing of variously claimed proteins *in vivo*.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants have now amended the claims to recite only MBNL1 as the protein to be expressed and administration of the MBNL1 vector by intramuscular injection. Thus, Applicants' amendments are found to be persuasive with regard to these particular aspects of the prior rejection of record. However, Applicants' amendments have not overcome #1-#2 detailed above.

Applicants' Arguments. Applicants argue that myotonia is a characteristic of myotonic dystrophia, whereas heart block, ocular cataracts, hypogonadism and nervous system dysfunction are all manifestations of the disease. Applicants argue that the examples show that MBNL1 contributes to DM pathogenesis in mice with a targeted deletion of Mbnl1 exon3, and that the mice show myotonia and develop distinctive ocular cataracts. Applicants further investigate alternative splicing related to MBNL and show that pre-mRNA targets are known to be misregulated in DM striated muscle are regulated by MBNL. See p. 6 of the Response.

Applicants further argue that Example 9 of the specification teaches FISH and IF analysis of DM1 brain, and teach that following FISH, sections were incubated with primary antibodies, including MBNL1, and that MBNL1 fluorescence intensity in the region of interest was determined for 20 cortical neuronal nuclei per subject, and that the specification provides guidance and support that treatment with MBNL1, as claims, results in reduction of DM. See p. 7 of the Response.

Response to Arguments. These arguments have been considered but are not persuasive. In particular, Example 9 is not within the scope of the claimed invention. This example teaches studying the expression and distribution of expanded poly (CUG) RNA in relation to putative RNA binding proteins in tissue from dead patients. The tissue obtained from DM1 patients were obtained by autopsy (see p. 39, lines 4+). This example teaches estimates of relative MBNL1 concentration in the nucleoplasm of DM1 nuclei patients, versus controls (p. 42, lines 10+) and teaches that patients with classical DM1 showed RNA foci in >85% of

cortical neurons (p. 42, lines 18+). Thus, this experiment shows teaches the expression of MBNL1 in DM1 patients, which is not within the scope of the invention because this example does not discuss *any* amelioration of any symptom of myotonic dystrophia by treatment with MBNL1 vectors. This example further does not teach treating the deceased patients' tissue with an rAAV vector comprising a promoter operably linked to a nucleic acid encoding MBNL1 protein. Thus, this example does not enable the claimed invention with regard to treatment of any other aspect of myotonic dystrophia, other than reduction of myotonia. As discussed previously, the state of the art of gene therapy is unpredictable, with regard to the particular therapeutic outcome, using a particular vector encoding a particular protein, and a particular mode of administration. In the instant case, the specification teaches a specific therapeutic outcome, the reduction of myotonia (see also, enabled scope and Example 4). The working examples of the specification teach that intramuscular injection of a rAAV vector comprising a promoter operably linked to a nucleic acid encoding MBNL1, whereby the expression of MBNL1 causes a reduction of myotonia. Treatment and reduction of myotonic dystrophia encompasses treatment or reduction of other symptoms that are not taught in the specification. The specification only provides guidance to show the reduction of myotonia. The state of the art provides support to show that one of skill in the art could not predictably arrive at a therapeutic result. The mice described in the specification show myotonia and develop distinctive ocular cataracts but this is not analogous to the instant case, where administration by intramuscular injection of an rAAV vector comprising a promoter operably linked to a nucleic acid encoding a MBNL1 protein would reduce symptoms, other than myotonia, such as the ocular cataracts. The specification provides no guidance with regard to treatment of the mice such that other symptoms of myotonia dystrophia would be reduced. Accordingly, the scope of enablement has been limited to reduction of myotonia.

Applicants' Arguments. Applicants argue that the specification provides enablement for the mis-splicing of variously claimed proteins, and point to p. 3, line 32, to show that misregulated alternative splicing in DM1 has been demonstrated for six pre-mRNAs. Applicants further argue that cTNA minigenes that are co-expressed in DM1 muscle cultures, or cTNT and IR pre-mRNAs co-expressed the CUG repeat RNA in normal cells and reproduce the aberrant splicing patterns observed for endogenous genes in DM cells (p. 8 of the Response). Applicants point to Example 5 and state that the experiments were carried out to determine whether MBNL proteins can alter the splicing patterns of pre-MRNAs known to be abnormally regulated in DM1 striated muscle, and that human and chicken cTNA and human IR minigenes were expressed with or without each of the three GFP-MBNL fusion proteins or with GFP alone, and that GFP-MBNL1, 2, and 3 strongly repressed inclusion of both human and chicken cTNT exon 5 in primary chicken skeletal muscle cultures, while expression of GFP to levels comparable to, or greater than, GFP-MBNL fusion proteins had no effect on splicing, and that in contrast to the inhibitor effect of MBNL on cTNT splicing, coexpression of MBNL family members with an IR minigene strongly induces exon inclusion. See p. 9 of the Response. Applicants argue that in Example 4, mice were intramuscularly injected with an rAAV vector comprising a promoter operably linked to a nucleic acid encoding MBNL1 protein and the left and right TAs were collected for total RNA preparation and assayed for recovery of normal Clcn1 pre-mRNA splicing patter, and the results show that the levels of abnormal splicing products were decreased while levels of the normal splicing product was increased, following rAAV1Myc-hMBNL1 injection, and thus, Applicants argue that they have taught that MBNL proteins regulate specific mRNA targets, and have established a nexus between the alternative splicing of cTNT and IR minigene by MBNL, and a method of treating an aberrant microsatellite expansion disease. See p. 9 of the Response.

Response to Arguments. These arguments have been fully considered but are not persuasive. In particular, the examples that Applicants point to, as noted previously, are *in vitro* examples, with cell types that are not necessarily representative of cells that are isolated from a mammal suffering from an aberrant microsatellite expansion disease. For example, the specification uses primary chicken skeletal muscle cells (Example 5), which are made to express human and chicken cTNT and human IR minigenes; however, these cells are not isolated from a mammal that has an aberrant microsatellite expansion disease, therefore it is unclear what nexus can be concluded from these *in vitro* results and a method of treating an aberrant microsatellite expansion disease *in vivo*. The lack of guidance provided by the specification with regard to a correlation between the *in vitro* results and a therapeutic *in vivo* outcome is not considered to be predictable, particularly in light of the unpredictable state of the art of gene therapy.

Additionally, Example 5, while showing a relationship between expression of MBNL genes and specific pre-mRNA targets, does not provide guidance with regard to reversing of mis-spliced genes, as required by the claims. That is, at the very most, this Example, as well as Example 4, only provides guidance to show potential repression or inhibition of the specific effect. A reversion would require that the mis-splice event had occurred and then the expression of MBNL1 would be sufficient to undo the mis-splicing in the specific gene. This is not the instant case. None of the working examples provide guidance to show once the specific pre-mRNA targets are spliced, they can be corrected by the method of the claimed invention. Therefore, it would have required the skilled artisan to practice undue experimentation in order to practice the embodiments of claims 4-8.

Accordingly, in view of the unpredictable state of the art of gene therapy, in particular, muscular gene therapy, with respect to the efficiency of gene transfer, protein expression, producing a therapeutic effect, the lack of specific teachings or guidance provided by the specification, specific guidance for any aspect of

treatment, other than reduction of myotonia in muscle tissue, the lack of any nexus between *in vitro* results regarding reversal of mis-splicing of variously claimed proteins and an *in vivo,* therapeutic result, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 103

The prior rejection of claim 13 under 35 U.S.C. 103(a) as being unpatentable over Synder *et al.* (**Human Gene Therapy**, 8: 1891-1900, November 1997) when taken with Miller *et al.* (**EMBO J.**, 19: 4439-4448, 2000, IDS) as evidenced by the Uniprot website "MBNL1" accessed online on May 10, 2009 is rendered moot in view of the cancellation of the claim.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 13 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Synder *et al.* (**Human Gene Therapy**, 8: 1891-1900, November 1997) when taken with Miller *et al.* (**EMBO J.**, 19: 4439-4448, 2000, IDS) as evidenced by the Uniprot website "MBNL1" accessed online on May 10, 2009.

Applicants' Arguments. Applicants argue that Synder does not teach or suggest a rAAV vector comprising a promoter operably linked to a nucleic acid encoding MBNL1 protein that can be used therapeutically and that the Miller reference does not cure the defects of the Synder reference. In particular, Applicants argue that the Miller reference teaches purifying the EXP proteins and does not teaches that MBNL1 would be useful in a pharmaceutical composition for therapeutic administration. Thus, Applicants argue that it would not be obvious to modify the teachings of Synder to produce an rAAV vector containing a transgene that encoded MBNL1 with a reasonable expectation of success. See pages 10-11 of the Response.

Response To Arguments. These arguments have been considered but are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In particular Synder provide guidance for utilizing an rAAV vector gene transfer into muscle fibers. Miller (as evidenced by the Uniprot website) teaches MBNL1. The Examiner asserts that it would have been *prima facie* obvious to modify the teachings of Synder to produce an rAAV vector containing a transgene that encodes MBNL1, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification to test the ability of the rAAV vector to express MBNL1, to study MBNL1 over-expression in vivo. One of ordinary skill would recognize that rAAV vectors provide an efficient means to stably transduce muscle fibers.

Rejection

Synder teach utilizing a recombinant rAAV vector for gene transfer into adult immunocompetent mice and teach that AAV vectors efficiently and stably transduce post-mitotic muscle fibers and myoblasts in vivo. See abstract. The vector taught by Synder contains the CMV immediate early gene promoter/enhancer (see p. 1892, col. 1-2, bridging sentence).

However, Synder do not specifically teach that the rAAV vector contains a transgene that encodes for MBNL1. However, prior to the time of the invention, Miller teach the sequence of MBNL1 (the Uniprot website is provided as evidence, see p. 4, References). Miller teach that MBNL1 is expressed in muscle tissue.

Accordingly, it would have been obvious to the skilled art to modify the teachings of Synder to produce an rAAV vector containing a transgene that encoded MBNL1, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification to test the ability of the rAAV vector to express MBNL1, to study MBNL1 over-expression in vivo. One of ordinary skill would recognize that rAAV vectors provide an efficient means to stably transduce muscle fibers.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Claim 34 is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632